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### Drugs that Alter Ventricular Repolarization

Some antiarrhythmic drugs achieve their desired effects by altering ventricular polarization, but with most drugs any effect on repolarization is an incidental side effect. Prolongation of repolarization (usually manifested as QT prolongation on the surface electrocardiogram) is sometimes benign or even antiarrhythmic (as with amiodarone, diltiazem, pentobarbital, and verapamil), but sometimes it is associated with arrhythmias, syncope, and death.

The normal quasiperiodic electrical activity of the heart is the result of the flow of ions through channels in the membranes of myocardial cells. Drugs affect ventricular repolarization by interfering with the opening and closing of these channels. The accompanying pages contain a [table](#) of various drugs and the concentrations at which they have been found to block some of these channels. Where available, the table also includes data as to the concentrations at which drugs bind to other receptors (*e.g.*, histamine receptors) of interest. The table began as a joint project with John Koerner at FDA, but we were unsuccessful in obtaining permission to post these public-domain data on the FDA Web site. Additional data are added as they are brought to my attention.

In addition, I am here posting a [paper](#) that also arose out of my collaboration with John Koerner. It did not pretend to describe FDA policy then, and it certainly doesn't now. Nevertheless, it couldn't be published while I remained at FDA. It was published this year (2002) in the *American Journal of Therapeutics* (9(2): 127-139), but except for correcting some reference details it had not been revised since mid-2000, and the long delay since its composition has left it more than a little dated. In particular, the limited predictive value of most preclinical studies has become increasingly evident, the indirectness of the connection between QT duration and arrhythmia has been realized, the Bazett formula has no currency outside of regulatory circles, and subject-specific (or at least study-population-specific) methods of QT interpretation have become the rule in serious work. I posted some [recommendations for electrophysiological workup](#) early in 2002, but I have decided not to attempt to keep these recommendations up to date with the ongoing science. News in this area will be posted on this page from time to time, with no commitment to thoroughness. A page of [Frequently-Asked Questions](#) goes over some of the same ground as the recommendations, but (because the FAQ genre imposes no requirements of completeness or even consistency) it is more likely to be kept up to date.

In late April 2002, I participated in **Phase5 Sciences' conference on Changes in Ventricular Repolarization: Implications for Drug Development**. This was an exciting meeting; the other speakers and panelists were Charles Antzelevitch, Arthur Brown, Timothy Callahan, Louis Cantilena, William Crumb, Marek Malik, Jean-Loup Parier, and Silvia Priori. To give a flavor of the discussion, I here summarize only one of the sessions.

To detect and characterize a drug-induced change in ventricular repolarization, several participants utilize 24-hour electrocardiograms, at least one at each subject's baseline and at least one during the subject's exposure to the suspect drug. Each such electrocardiogram captures about  $10^5$  beats, and different subsets of the beats are used in different participants' analyses. To facilitate description of the different approaches, I use a taxonomy of ECG complexes that is in some ways a logical union of the taxonomies used by the speakers:

- Some beats (**Group A**) are so distorted by electrical artifact that they are not amenable to measurement.
- Consider the beats not in Group A. After a change in heart rate, the QT interval is commonly observed to take about 2 minutes to achieve a new steady state. For this reason, one can for each beat examine the range of heart-rate variation observed during the previous few minutes. Beats preceded by more-than-minimal heart-rate variation are segregated into **Group B**.
- Consider the beats not in Group A or Group B. Even though each such beat was preceded by a period of stable heart rate, some beats might have been preceded by a few minutes of more-than-minimal QT variation. Such beats constitute **Group C**, while the remaining beats constitute **Group D**.

To be able to detect drug-induced changes in repolarization, Malik first characterizes each subject's personal QT-RR relationship, using the beats of Groups C and D in a recording made at baseline. Reasoning by analogy from *in vitro* Brown suggested that a plausibly more stable estimate might be derived if Malik's analysis were restricted to beats from

#### Group D.

Rather than attempt to describe a subject's QT-RR relationship in isolation, Parier and Callahan look at the frequency distributions of rate-corrected QT duration, comparing the baseline distribution of beats in Groups B-C-D to the distribution seen when beats from the same groups are collected during drug treatment.

Antzelevitch noted that the compounds that in wedge preparations induce harmless prolongation of repolarization can be distinguished from those that induce arrhythmias by experiments in which the basic cycle length is abruptly changed. During studies of a proarrhythmic compound, sometimes the preparation exhibits unremarkable behavior at either of the steady-state cycle lengths, but early afterdepolarizations are seen for a minute or two after the change in rate. Returning to the 24-hour human electrocardiograms, some participants speculated on the basis of Antzelevitch's observations that although beats of Group B might be uninterpretable in attempts to define the QT-RR relationship, these beats might turn out to hold the information distinguishing harmless QT prolongation from proarrhythmia.

[Home](#)

Page revised: 03/03/2003 19:51